Infant Fever: An Ongoing Clinical Conundrum

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Learning objectives:

1. Discuss the need for prompt and accurate diagnosis and treatment of serious bacterial illness (SBI) in infants < 2 mos of age

2. Identify how the approach to neonatal fever has changed over time

3. Choose appropriate evidence-based clinical tests to establish the etiology of fever in infants less than 2 months of age, as well as to utilize appropriate treatment

Outline

- Changing epidemiology of SBI in infants
- Risk stratification tools and testing
- UK infant fever protocol
- AAP guideline
- Future directions

So why is this such a challenging clinical problem?

- History and physical exam on infants can be difficult
- Missed diagnoses can lead to very poor outcomes
- Take into account in utero, perinatal, and postnatal sources
- Tests and algorithms need to be nearly 100% accurate – you don't want to be the provider/parent of the infant whose SBI was missed
- The infant's immune system functions differently than in older kids

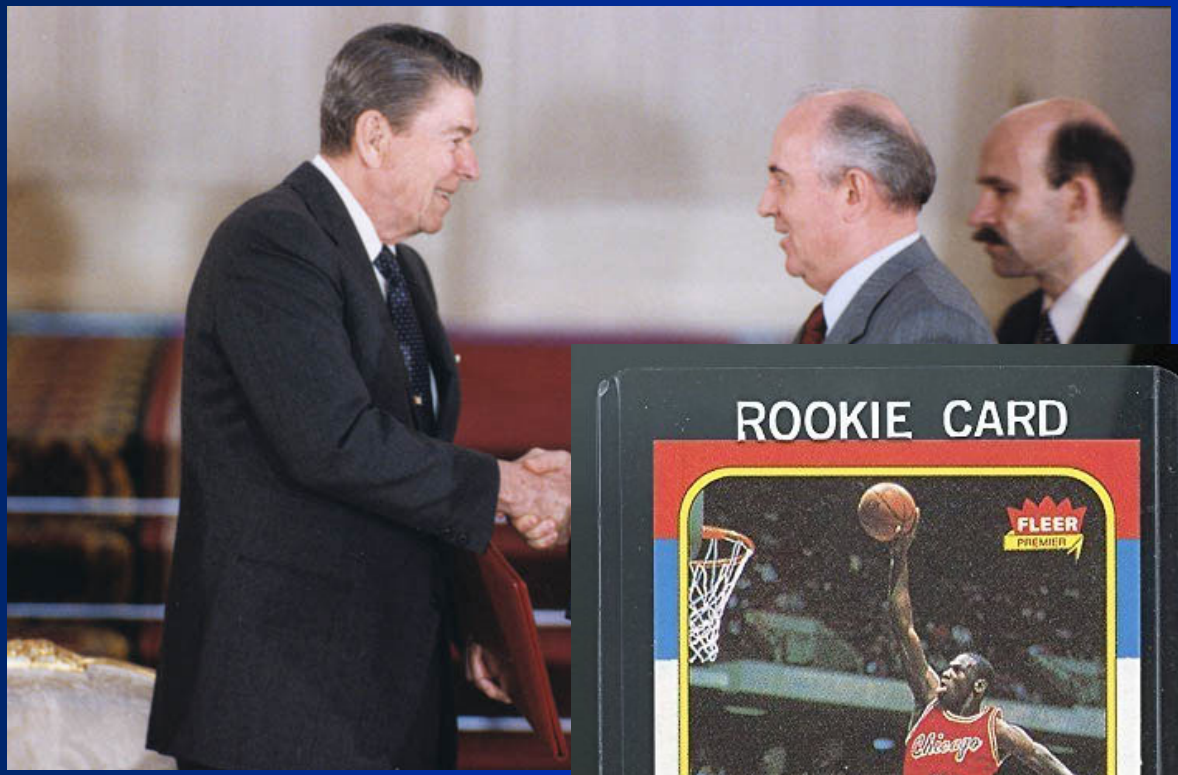
Serious bacterial illness (**SBI**) is usually defined as:

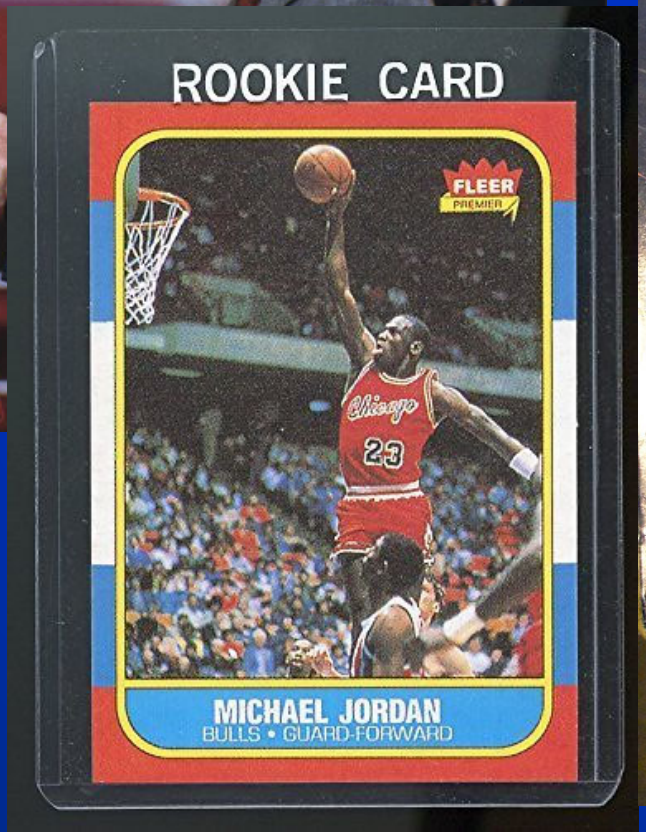
1. Urinary tract infection
2. Bacteremia
3. Meningitis

} **IBI**

Focal infection (skin, soft tissue, joints, umbilicus) is usually considered separately as it is easier to diagnose by exam alone

Pneumonia is also considered separately due to the prevalence of viral etiologies




ROOKIE CARD
FLEER
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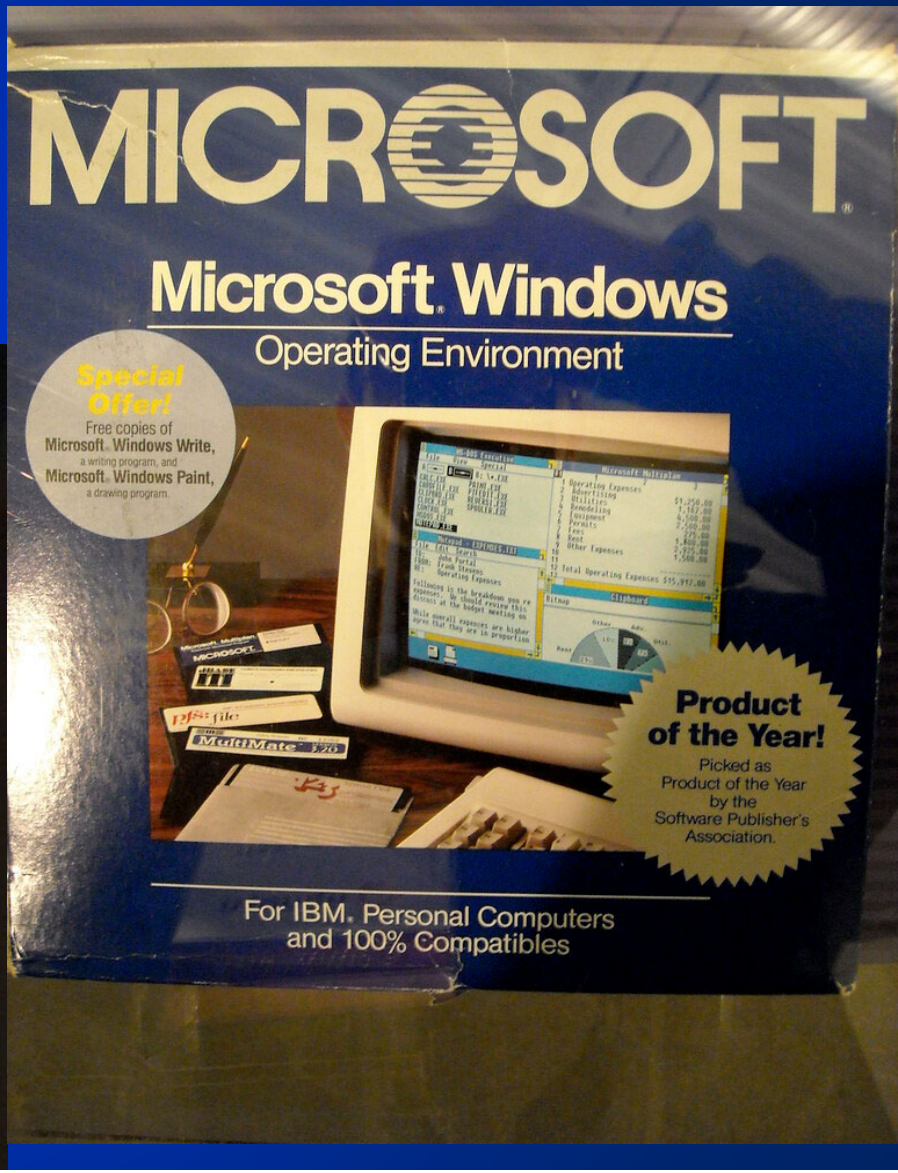
23
MICHAEL JORDAN
BULLS • GUARD-FORWARD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For IBM Personal Computers and 100% Compatibles

1985


BACK
TO THE FUTURE
OUTATIME

Etiology of SBIs in 1985:

<28 days: GBS, E. Coli, Listeria, HSV

1 – 11 months: H. influenzae type B, Neisseria meningitidis, Pneumococcus

Immunization schedule in 1985:

2 months: DTP, OPV
4 months: DTP, OPV
6 months: DTP
15 months: MMR
18 months: DTP, OPV
4 years: DTP, OPV
Every 10 years after: Td

Treatment of neonatal fever in 1985:

- All infants less than 90 days were hospitalized
- All infants got urine, blood and CSF cultures
- Ampicillin and gentamycin up until 30 days
- Ampicillin and cefotaxime or cefuroxime or ceftriaxone 31-90 days
- Treat for 48 hours negative cultures minimum

Other things that were different in 1985:

- No real time PCR
- No BACTEC systems
  - Other than blood, cultures were read once a day in the morning
- ID and sensitivities often took 24 hours each as cultures needed time to grow

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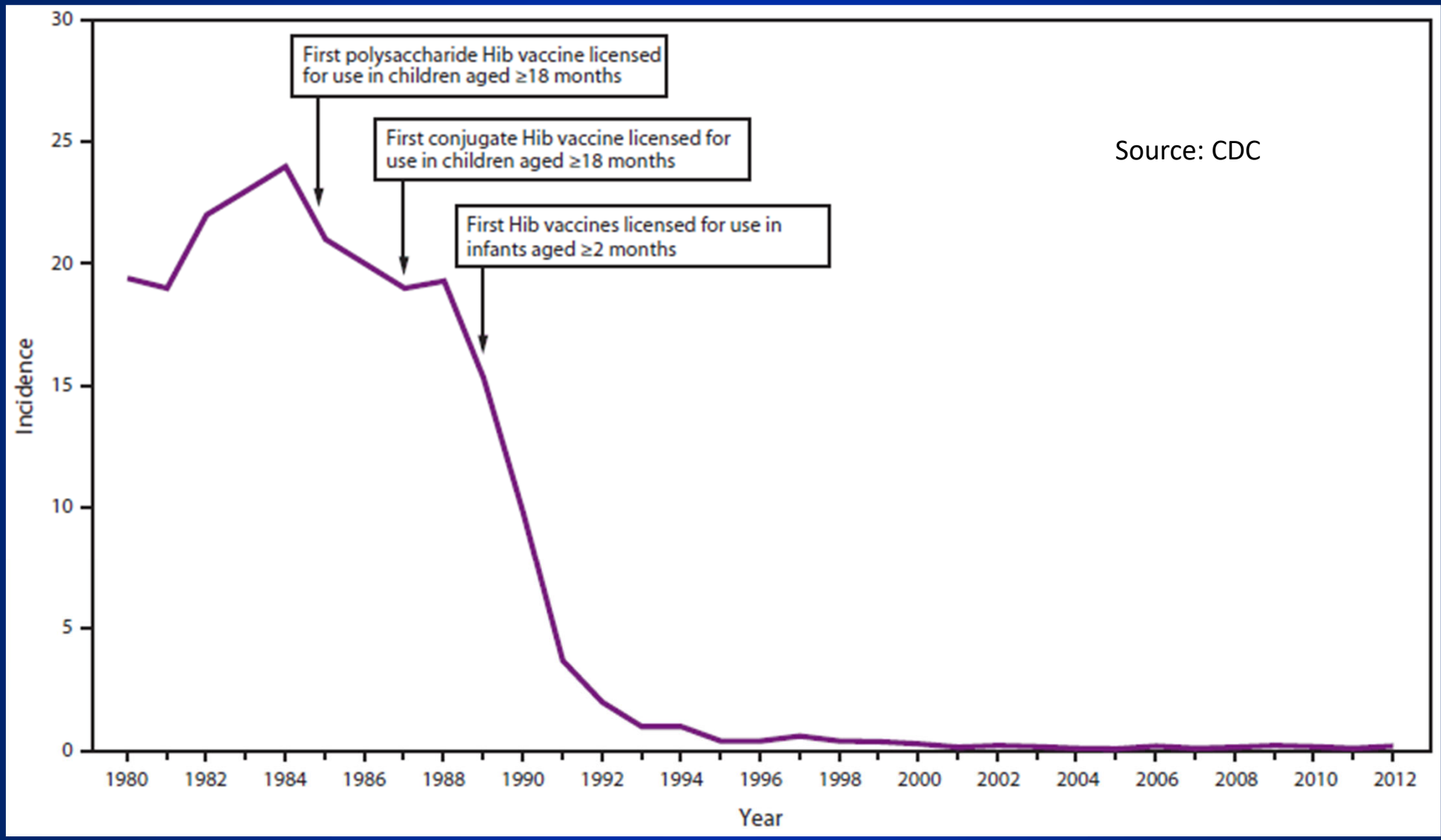
NDC 49281-545-03
Haemophilus b
Conjugate Vaccine
(Tetanus Toxoid Conjugate)
ActHIB®
For children 2 months through 5 years of age
Hib
5 VIALS
1 Dose
each
℞ only
SANOFI PASTEUR
Saline Diluent
(0.4% Sodium

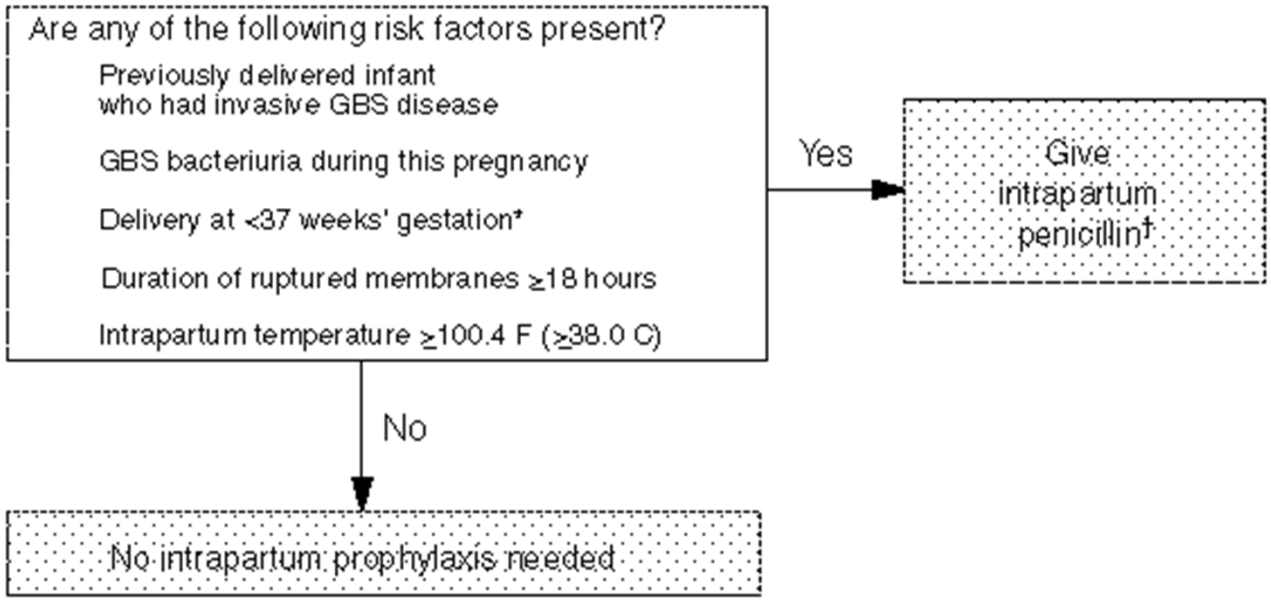
1985


First polysaccharide Hib vaccine licensed for use in children aged ≥18 months
First conjugate Hib vaccine licensed for use in children aged ≥18 months
First Hib vaccines licensed for use in infants aged ≥2 months
Incidence
30
25
20
15
10
5
0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
2010
2012
Year

Source: CDC

1996

FIGURE 2. Algorithm for prevention of early-onset of group B streptococcal (GBS) disease in neonates, using risk factors



*If membranes ruptured at <37 weeks' gestation, and the mother has not begun labor, collect group B streptococcal culture and either a) administer antibiotics until cultures are completed and the results are negative or b) begin antibiotics only when positive cultures are available.
†Broader spectrum antibiotics may be considered at the physician's discretion, based on clinical indications.


NDC 0005-1970-67
Pneumococcal 7-valent Conjugate Vaccine
(Diphtheria CRM197 Protein)
Prevnar™
For Intramuscular Use Only
Rx only
5 X 0.5 mL Vials
CONTAINS NO PRESERVATIVE
WYETH LEDERLE

2000

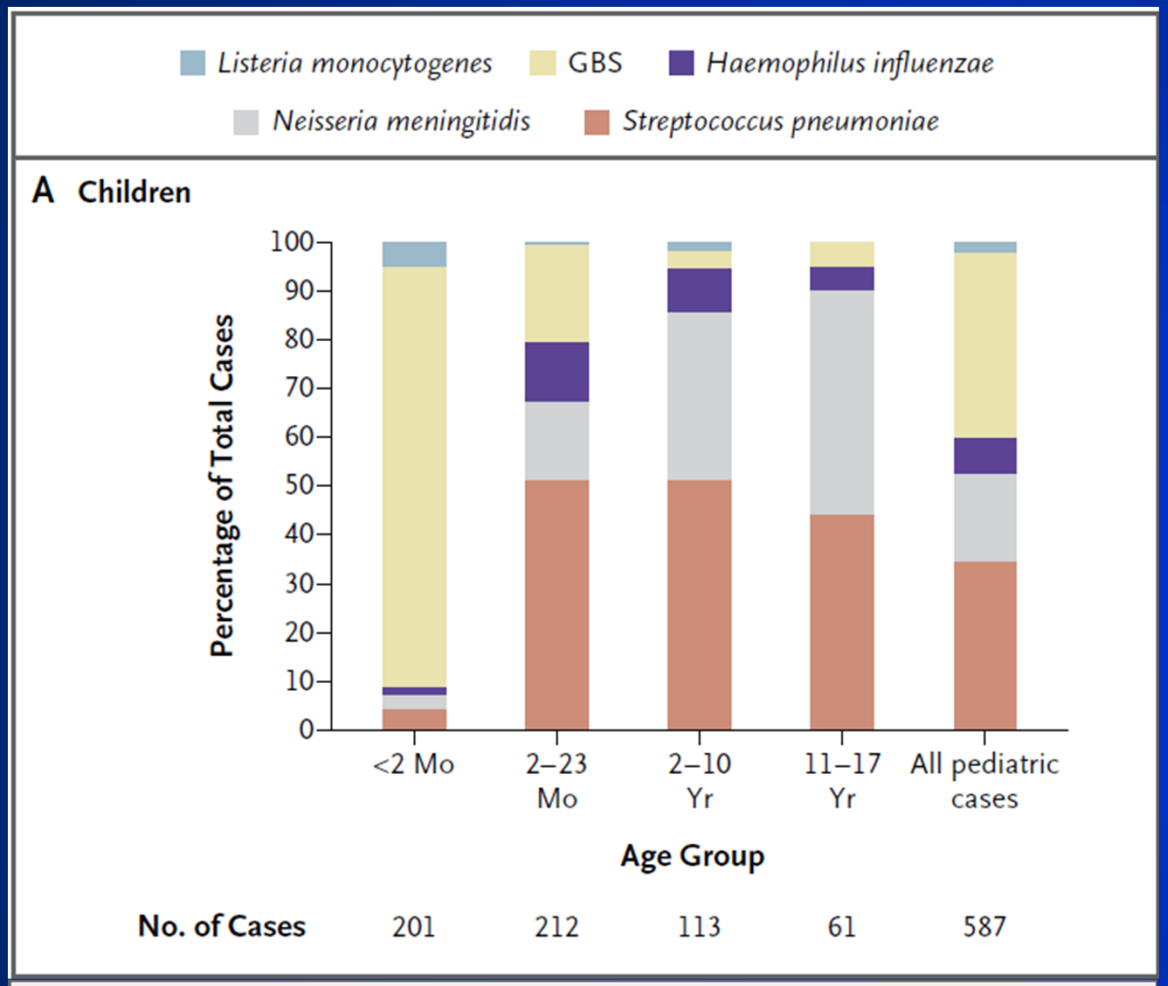
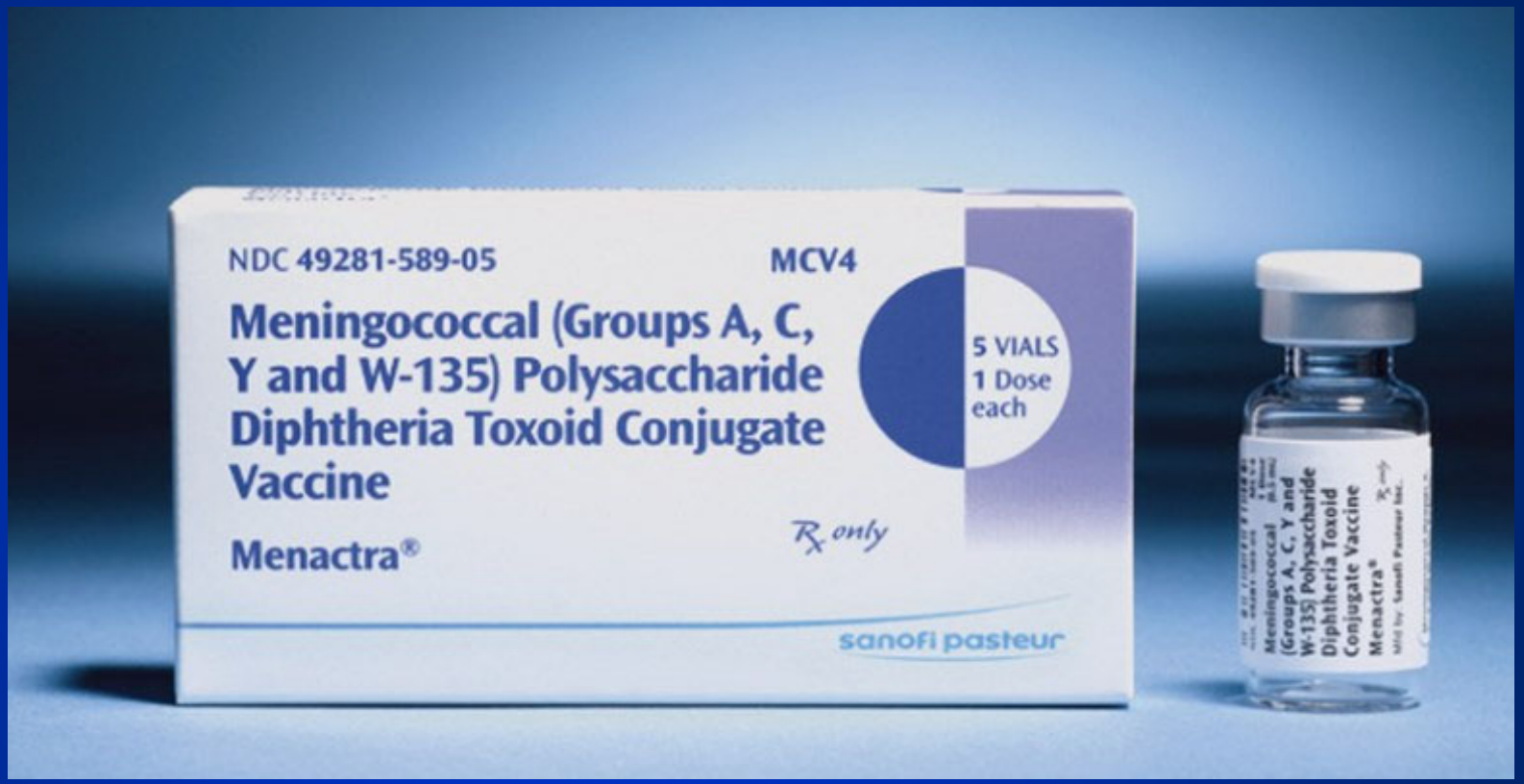


Figure 1. Proportions of the 1670 Cases of Bacterial Meningitis Reported in 2003–2007 Caused by Each Pathogen, According to Age Group.

Prevnar was in very short supply after its initial release

Thigpen et. al.
NEJM 2011
364:2016-25


NDC 49281-589-05
MCV4
Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine
5 VIALS
1 Dose
each
℞ only
Menactra®
sanofi pasteur
Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine Menactra®

2005

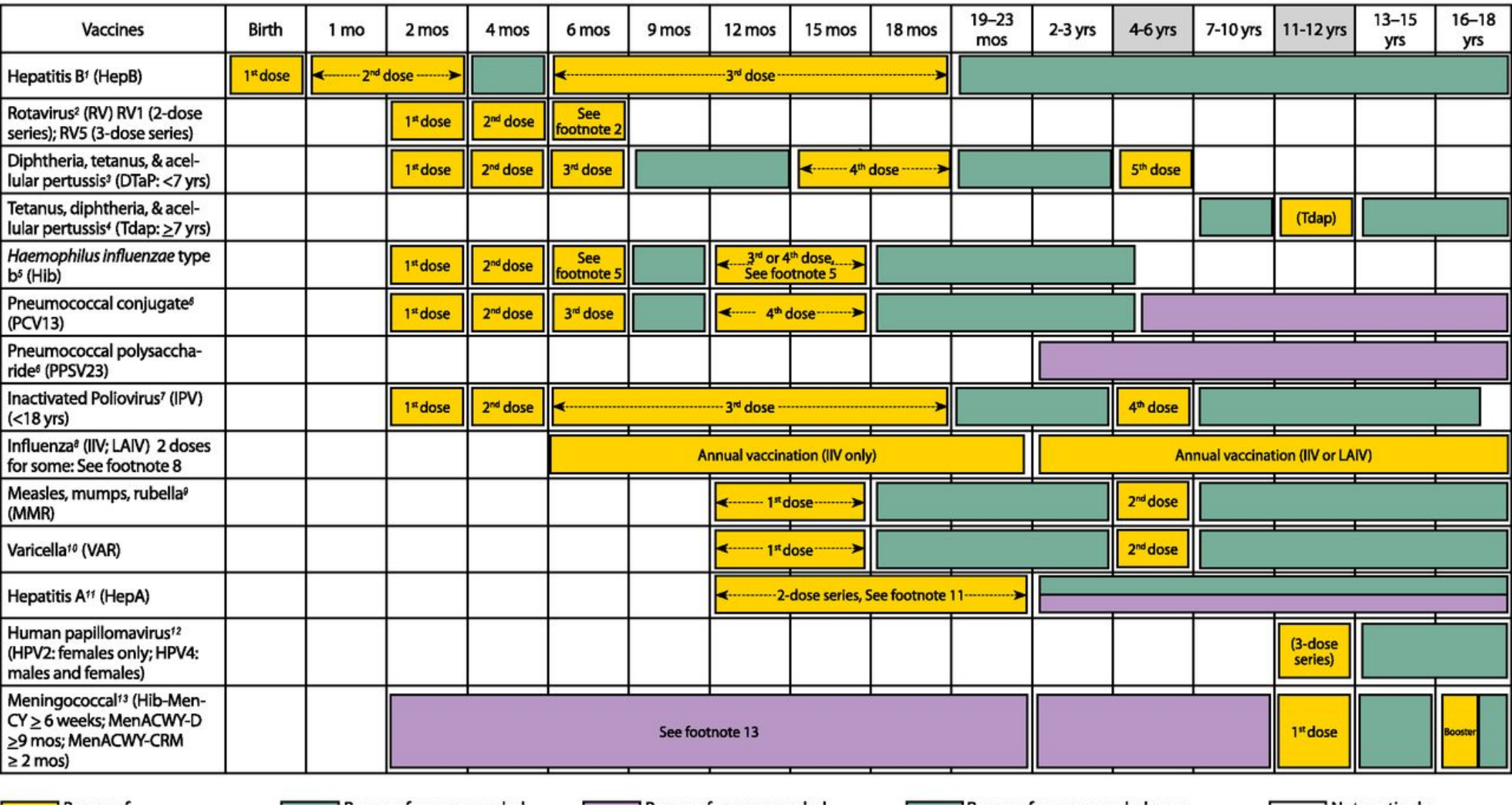

Prevnar 13®
Pneumococcal 13-valent Conjugate Vaccine
(Diphtheria CRM197 Protein)

2010

2015


Meningococcal
Group B Vaccine
Trumenba™
For use in individuals
10 through 25 years of age
5 One-Dose (0.5 mL)
Prefilled Syringes
Pfizer
FOR INTRAMUSCULAR USE ONLY
Rx only
Meningococcal
Group B Vaccine
Trumenba
Pfizer
STORE
SYRINGES
HORIZONTALLY

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 1. To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are in bold.



Questions?

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All these new vaccines made a big difference in children older than 2 months of age, and the incidence of all of these now vaccine-preventable diseases decreased dramatically in the general population.

But what about the as-yet unvaccinated infant **under 2 months of age**?

These infants were still just as susceptible to these diseases

And pediatricians noted they were doing a lot more sepsis workups which were totally normal

So the key question became:

How did the dramatically decreased incidence of these diseases in the general population, as well as the advent of better diagnostic technology change our approach to the febrile infant?

Diagnostic tools in 1985:

1. WBC
2. UA
3. Band count

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The Journal of Pediatrics
Volume 107, Issue 6, December 1985, Pages 855-860

Original article

Identification of infants unlikely to have serious bacterial infection although hospitalized for suspected sepsis

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Available online 8 March 2006.

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https://doi.org/10.1016/S0022-3476(85)80175-X

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Rochester criteria (1985)

Who was really septic?

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Rochester criteria:

Apply to well-appearing infants 60 days old or less who are previously healthy and who have no focal infection

Infants were low risk for SBI if:

1. WBC between 5,000 and 15,000
2. Band count < 1,500
3. < 10 WBC/hpf on urine micro

< 5 WBC/hpf on stool added in 1994

Outpatient treatment of febrile infants 28 to 89 days of age with intramuscular administration of ceftriaxone

M N Baskin, E J O'Rourke, G R Fleisher

Journal of Pediatrics 1992, 120 (1): 22-7

STUDY OBJECTIVE: To determine the outcome of outpatient treatment of febrile infants 28 to 89 days of age with intramuscular administration of ceftriaxone.

DESIGN: Prospective consecutive cohort study.

SETTING: Urban emergency department.

PATIENTS: Five hundred three infants 28 to 89 days of age with temperatures greater than or equal to 38 degrees C who did not appear ill, had no source of fever detected on physical examination, had a peripheral leukocyte count less than 20 x 10(9) cells/L, had a cerebrospinal fluid leukocyte count less than 10 x 10(6)/L, did not have measurable urinary leukocyte esterase, and had a caretaker available by telephone. Follow-up was obtained for all but one patient (99.8%).

INTERVENTION: After blood, urine, and cerebrospinal fluid cultures had been obtained, the infants received 50 mg/kg intramuscularly administered ceftriaxone and were discharged home. The infants returned for evaluation and further intramuscular administration of ceftriaxone 24 hours later; telephone follow-up was conducted 2 and 7 days later.

Boston criteria (1992)
Who can we treat outpatient?

Boston criteria:

Apply to infants 28 to 89 days of age who were well-appearing and who have no focal infection

Infants were low risk for SBI if:

1. WBC < 20,000
2. < 10 WBC on **CSF**
3. Negative leukocyte esterase on UA

The New England
Journal of Medicine

Volume 329 NOVEMBER 11, 1993 Number 20

OUTPATIENT MANAGEMENT WITHOUT ANTIBIOTICS OF FEVER IN SELECTED INFANTS

M. Douglas Baker, M.D., Louis M. Bell, M.D., and Jeffrey R. Avner, M.D.

Abstract *Background.* In many academic centers it is standard practice to hospitalize all febrile infants younger than two months of age, whereas in community settings such infants are often cared for as outpatients.

Methods. We conducted a controlled study of 747 consecutive infants 29 through 56 days of age who had temperatures of at least 38.2°C. After a complete history taking, physical examination, and sepsis workup, the 460 infants with laboratory or clinical findings suggestive of serious bacterial illness were hospitalized and treated with antibiotics. The screening criteria for serious bacterial illness included a white-cell count of at least 15,000 per cubic millimeter, a spun urine specimen that had 10 or more white cells per high-power field or that was positive on bright-field microscopy, cerebrospinal fluid with a white-cell count of 8 or more per cubic millimeter or a positive Gram's stain, or a chest film showing an infiltrate. The 287 infants who had unremarkable examinations and normal laboratory results were assigned to either inpatient observation without antibiotics (n = 148) or outpatient care without antibiotics but with reexaminations after 24 and 48 hours (n = 139).

Results. Serious bacterial illness was diagnosed in 65 infants (8.7 percent). Of these 65 infants, 64 were identified by our screening criteria for inpatient care and antibiotic treatment (sensitivity = 98 percent; 95 percent confidence interval, 92 to 100). Of the 287 infants assigned to observation and no antibiotics, 286 (99.7 percent) did not have serious bacterial illness. Only two infants assigned to outpatient observation were subsequently admitted to the hospital; neither was found to have a serious illness. Outpatient care without antibiotics of the febrile infants at low risk for serious illness resulted in a savings of about $3,100 per patient.

Conclusions. With the use of strict screening criteria, a substantial number of febrile one-to-two-month-old infants can be cared for safely as outpatients and without antibiotics. (N Engl J Med 1993;329:1437-41.)

Philadelphia criteria (1993)

Who can we treat outpatient and with no antibiotics?

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Philadelphia criteria:

Apply to infants 29 to 56 days of age regardless of appearance

Infants were low risk for SBI if:

1. WBC < 15,000
2. < 10 WBC/hpf on urine micro
3. < 8 WBC on **CSF** and negative Gram stain
4. CXR clear

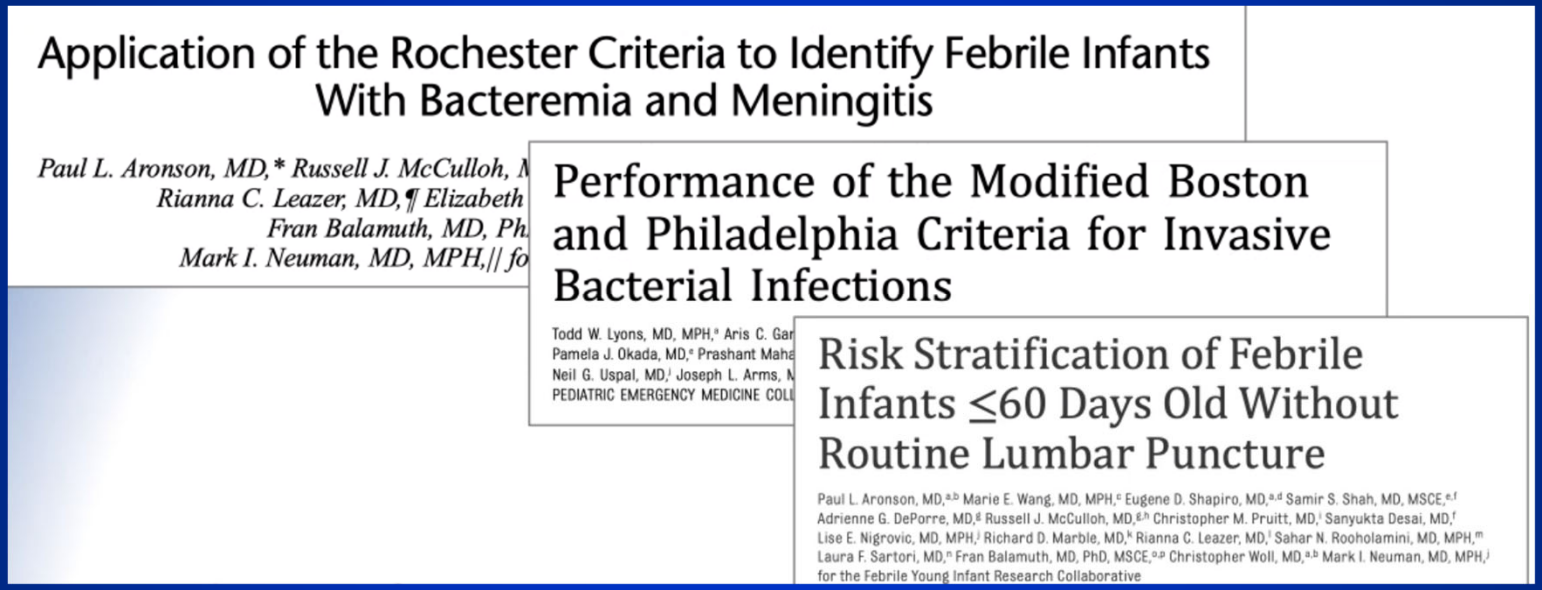
Guidelines (1993)

TABLE 1. Three Main Protocols for the Management of the Well-Appearing Febrile Infants With an Otherwise Normal Physical Examination

	Philadelphia[8]	Rochester[9]	Boston[10]
Age, d	29–60	<60	28–89
Temperature, °C	≥38.0*		≥38.0
Laboratory parameters indicating low-risk status	• WBC <15,000/μL • Band-neutrophil ratio <0.2 • UA < 10 WBCs/HPF • Urine Gram stain negative • CSF <8 WBCs/μL • CSF Gram stain negative • Chest x-ray without infiltrate (if obtained) • Stool without blood, few or no WBCs on smear, if diarrhea	• WBC >5000 and <15,000/μL • Absolute band count <1500/μL • UA ≤10 WBCs/HPF • Stool ≤5 WBCs/HPF on smear, if diarrhea • Chest x-ray negative, if indicated	• WBC <20,000/μL • UA <10 WBCs/HPF • CSF <10 WBCs/μL • Chest x-ray negative, if obtained
Recommendations for low-risk patients	Home No antibiotics Follow-up required	Home No antibiotics Follow-up required	Home Antibiotics administered Follow-up required
Reported statistics			
Sensitivity	100%†	92%	Not available
Specificity	27%†	50%	95%
PPV	13%†	12%	Not available
NPV	100%†	99%	Not available

Meehan et al. (2010) *Pediatr Emerg Care*

Guidelines applied today



Rochester sensitivity IBI – 81%
Philadelphia sensitivity IBI – 71.7%%
Boston sensitivity IBI – 62.7%

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The Rochester, Boston and Philadelphia criteria were developed between 1985 and 1993

By 2000, HiB was under control, but pneumococcal and meningococcal disease were not

How did the development of new vaccines change the approach to febrile infants?

Bedside Procalcitonin and C-Reactive Protein Tests in Children With Fever Without Localizing Signs of Infection Seen in a Referral Center

Annick Galetto-Lacour, MD; Samuel A. Zamora, MD; and Alain Gervaix, MD

ABSTRACT. *Objective.* To assess the value of bedside tests for predicting the occurrence of severe bacterial infections (SBIs) in children with fever without source.

Methods. We conducted a prospective study of 99 children, aged 7 days to 36 months, who were seen for fever >38°C and no localizing sign of infection at the emergency department of the University Children's Hospital of Geneva. Blood procalcitonin (PCT), C-reactive protein (CRP), and interleukin-6 (IL-6) values were determined using rapid tests and were compared with the total white blood cell (WBC) count with differential and clinical score. Specificity, sensitivity, predictive values, and multilevel likelihood ratios (LRs) with posttest probabilities of disease were calculated.

Results. Twenty-nine (29%) children received a diagnosis of having an SBI. PCT had the best sensitivity (93%) and negative predictive value (96%). Band count had the best specificity (93%), but its positive predictive value was only 38%. Multilevel LRs revealed that a PCT concentration <0.5 ng/mL (LR: 0.093) almost ruled out SBI (posttest probability of disease: 3.7%) in 54 (54%) subjects, whereas a value >2 ng/mL (LR: 5.2) increased the probability of SBI to 68% in 19 (19%) children. For CRP, values <40 mg/L (LR: 0.263) and >100 mg/L (LR: 14.483) generated posttest probabilities for SBI of 9.7% (61 subjects) and 86.5% (14 subjects), respectively. For WBC count, the posttest probabilities of SBI were modestly changed from the pretest prevalence.

Conclusions. PCT and CRP performed better than IL-6, WBC, and/or band count in predicting the occurrence of SBI. PCT and CRP bedside tests may be useful tools for emergency and private practice doctors and should be considered in the initial work-up of children with fever without source. *Pediatrics* 2003;112:1054–1060; *interleukin-6, procalcitonin, C-reactive protein, bacterial infection, fever without source, pediatrics, pyelonephritis.*

ABBREVIATIONS. ED, emergency department; SBI, serious bac

Fever is a common cause of childhood visits to emergency departments (EDs) and pediatric offices.[1,2] In the majority of children, a benign infection is diagnosed after a good history and a careful examination that reveal the site of infection. In rare instances, especially in infants, infection is manifested only by fever and vague or nonspecific signs and symptoms, and no focus is evidenced after the clinical examination. Although most of these children also have benign and self-limited illness, a few are at risk of developing a severe bacterial infection (SBI) such as bacteremia, meningitis, or pyelonephritis,[3] the missed diagnosis of which is a common source of malpractice suits.[4] The problem faced by the physician is to find clues that could distinguish the few who have SBI from the vast majority of children who have benign infection. Practical guidelines have been proposed by a panel of experts for the treatment of infants and children with fever without source (FWS).[5] In these recommendations, algorithms based on clinical and laboratory evaluation have been proposed, but in practice, the decision to treat the nontoxic-appearing child is based largely on a white blood cell (WBC) count >15 g/L or band form >1.5 g/L. The diagnostic tests called for in the guidelines are sometimes difficult to obtain for many physicians in private practice, are time-consuming, and require a trained technician. It therefore is not surprising that compliance with these guidelines is low[6] and varies widely between private office settings and hospital EDs.[7] Thus, for many authors, these recommendations are inadequate and favor overhospitalization and overprescription of antibiotics, leading to the selection of resistant bacteria.[8,9] Furthermore, both measures encompass substantial costs.

Advent of additional biomarkers (2003)

- Procalcitonin
- CRP
- IL-6

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Original article

Validation of a laboratory risk index score for the identification of severe bacterial infection in children with fever without source

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Published Online First 1 June 2010

ABSTRACT

Objective The identification of severe bacterial infection (SBI) in children with fever without source (FWS) remains a diagnostic problem. The authors previously developed in their Swiss population a risk index score, called the Lab-score, associating three independent predictors of SBI, namely C reactive protein (CRP), procalcitonin (PCT) and urinary dipstick. The objective of this study was to validate the Lab-score in a population of children with FWS different from the derivation model.

Methods A prospective study, conducted in Padova, on 408 children aged 7 days to 36 months with FWS was recently published. PCT, CRP, white blood cell count (WBC) and urinary dipstick were determined in all children. The Lab-score was applied to this population and the diagnostic characteristics for the detection of SBI were calculated for the Lab-score and for any single variable used in the Italian study.

Results For the identification of SBI, the sensitivity of a score ≥3 was 86% (95% CI 77% to 92%) and the specificity 83% (95% CI 79% to 87%). The area under the receiver operating characteristic curve for the Lab-score (0.91) was significantly superior to that of any single variable: 0.71 for WBC, 0.86 for CRP and 0.84 for PCT. The Lab-score performed better than other laboratory markers, even when applied to children of different age groups (<3 months, 3–12 months and >12 months). The results obtained in this validation set population were comparable with those of the derivation set population.

Conclusions This study validated the Lab-score as a valuable tool to identify SBI in children with FWS.

What is already known on this topic

- Current US guidelines in the management of young children with fever without source (FWS) are rarely followed by paediatricians because of time constraints.
- Biological markers such as procalcitonin (PCT) and C reactive protein (CRP) have been shown to be quick and reliable predictors of severe bacterial infection (SBI).
- A risk index score of SBI associating PCT, CRP and urinary dipstick has been recently published and showed to be superior to any individual markers.

What this study adds

- This risk index score has been now validated in a large external cohort of young children with FWS.
- This risk index score of SBI is a quick and useful tool for the management of FWS in emergency departments.

This risk index score was the most accurate tool differentiating children with and without SBI.

Lab score (2010)

First to use PCT and CRP in assessment of febrile infants

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Lab score (2010):

Infants were 7 days to 36 months old

Score >=3 identified SBI with a sensitivity of 86% and a specificity of 83%

Table 1 Lab-score

Predictor	Points
PCT (ng/ml)	
<0.5	0
≥0.5	2
≥2	4
CRP (mg/l)	
<40	0
40–99	2
≥100	4
Urine dipstick*	
Negative	0
Positive	1

*Positive urine dipstick: positive leucocytes esterase or nitrite test result.
CRP, C reactive protein; PCT, procalcitonin.

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Accuracy of a sequential approach to identify young febrile infants at low risk for invasive bacterial infection

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ABSTRACT

Introduction Much effort has been put in the past years to create and assess accurate tools for the management of febrile infants. However, no optimal strategy has been so far identified. A sequential approach evaluating, first, the appearance of the infant, second, the age and result of the urinanalysis and, finally, the results of the blood biomarkers, including procalcitonin, may better identify low risk febrile infants suitable for outpatient management.

Objective To assess the value of a sequential approach ('step by step') to febrile young infants in order to identify patients at a low risk for invasive bacterial infections (IBI) who are suitable for outpatient management and compare it with other previously described strategies such as the Rochester criteria and the Lab-score.

Methods A retrospective comparison of three different approaches (step by step, Lab-score and Rochester criteria) was carried out in 1123 febrile infants less than 3 months of age attended in seven European paediatric emergency departments. IBI was defined as isolation of a bacterial pathogen from the blood or cerebrospinal fluid.

Results Of the 1123 infants (IBI 48; 4.2%), 488 (43.4%) were classified as low-risk criteria according to the step by step approach (vs 693 (61.7%) with the Lab-score and 458 (40.7%) with the Rochester criteria). The prevalence of IBI in the low-risk criteria patients was 0.2% (95% CI 0% to 0.6%) using the step by step approach; 0.7% (95% CI 0.1% to 1.3%) using the Lab-score; and 1.1% (95% CI 0.1% to 2%) using the Rochester criteria. Using the step by step approach, one patient with IBI was not correctly classified (2.0%, 95% CI 0% to 6.12%) versus five using the Lab-score or Rochester criteria (10.4%, 95% CI 1.76% to 19.04%).

Conclusions A sequential approach to young febrile infants based on clinical and laboratory parameters, induding procalcitonin, identifies better patients more suitable for outpatient management.

it is necessary to identify those patients at low risk for SBI and, mainly, invasive bacterial infection (IBI).

Several attempts have been made in order to identify patients with low-risk criteria for SBI.[3–6] Usually, low-risk criteria include a combination of clinical and laboratory data. However, the contribution of each parameter in predicting SBI is different. As the most common SBI in this age group is urinary tract infection (UTI),[4] the yield of urinalysis, compared with blood markers or other tests, is the highest. Blood biomarkers are more helpful in predicting bacteraemia or meningitis. However, the value of these tests is controversial. Recent studies have shown that white blood cell (WBC) count has a poor value in the diagnosis of bacteraemia and other bacterial infections in these infants.[7 8] In fact, WBC count has been relegated in the more recently developed scores to identify patients at higher risk for SBI[9 10] and newer biomarkers as C reactive protein (CRP)[10] and, mainly, procalcitonin (PCT)[11] seem to be more useful to identify febrile young infants with bacterial infections.[2 12]

The traditional approach to these infants has included the assessment of both clinical and laboratory data together for decision-making on the most adequate management (ie, admission and/or treatment). A sequential approach ('step by step') which takes into account in the first instance the appearance of the infant, and in sequence the age, the result of the urinanalysis and, finally, the results of the blood biomarkers (including PCT) may be a more practical approach for decision-making regarding these infants.

The main objective of this study was to assess the accuracy of a step by step approach to febrile young infants in order to rule in and, mainly, rule out IBIs, thus identifying infants suitable for an outpatient management.

The secondary objective was to compare this approach with other previously reported strategies

Step by step approach (2014):

Better than either Lab-score or Rochester criteria in identifying SBI in infants less than 3 months of age

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Validation of the "Step-by-Step" Approach in the Management of Young Febrile Infants

Borja Gomez, MD,[a,b] Santiago Mintegi, MD, PhD,[a,b] Silvia Bressan, MD, PhD,[c] Liviana Da Dalt, MD,[d] Alain Gervaix, MD,[e] Laurence Lacroix, MD,[e] on behalf of the European Group for Validation of the Step-by-Step Approach

abstract

BACKGROUND: A sequential approach to young febrile infants on the basis of clinical and laboratory parameters, including procalcitonin, was recently described as an accurate tool in identifying patients at risk for invasive bacterial infection (IBI). Our aim was to prospectively validate the Step-by-Step approach and compare it with the Rochester criteria and the Lab-score.

METHODS: Prospective study including infants ≤90 days with fever without source presenting in 11 European pediatric emergency departments between September 2012 and August 2014. The accuracy of the Step-by-Step approach, the Rochester criteria, and the Lab-score in identifying patients at low risk of IBI (isolation of a bacterial pathogen in a blood or cerebrospinal fluid culture) was compared.

RESULTS: Eighty-seven of 2185 infants (4.0%) were diagnosed with an IBI. The prevalence of IBI was significantly higher in infants classified as high risk or intermediate risk according to the Step by Step than in low risk patients. Sensitivity and negative predictive value for ruling out an IBI were 92.0% and 99.3% for the Step by Step, 81.6% and 98.3% for the Rochester criteria, and 59.8% and 98.1% for the Lab-score. Seven infants with an IBI were misclassified by the Step by Step, 16 by Rochester criteria, and 35 by the Lab-score.

CONCLUSIONS: We validated the Step by Step as a valuable tool for the management of infants with fever without source in the emergency department and confirmed its superior accuracy in identifying patients at low risk of IBI, compared with the Rochester criteria and the Lab-score.

FREE

Pediatrics August 2016

Step by step approach (2016):

Again, better than either Lab-score or Rochester criteria in identifying SBI in infants less than 3 months of age – this time in a prospective study

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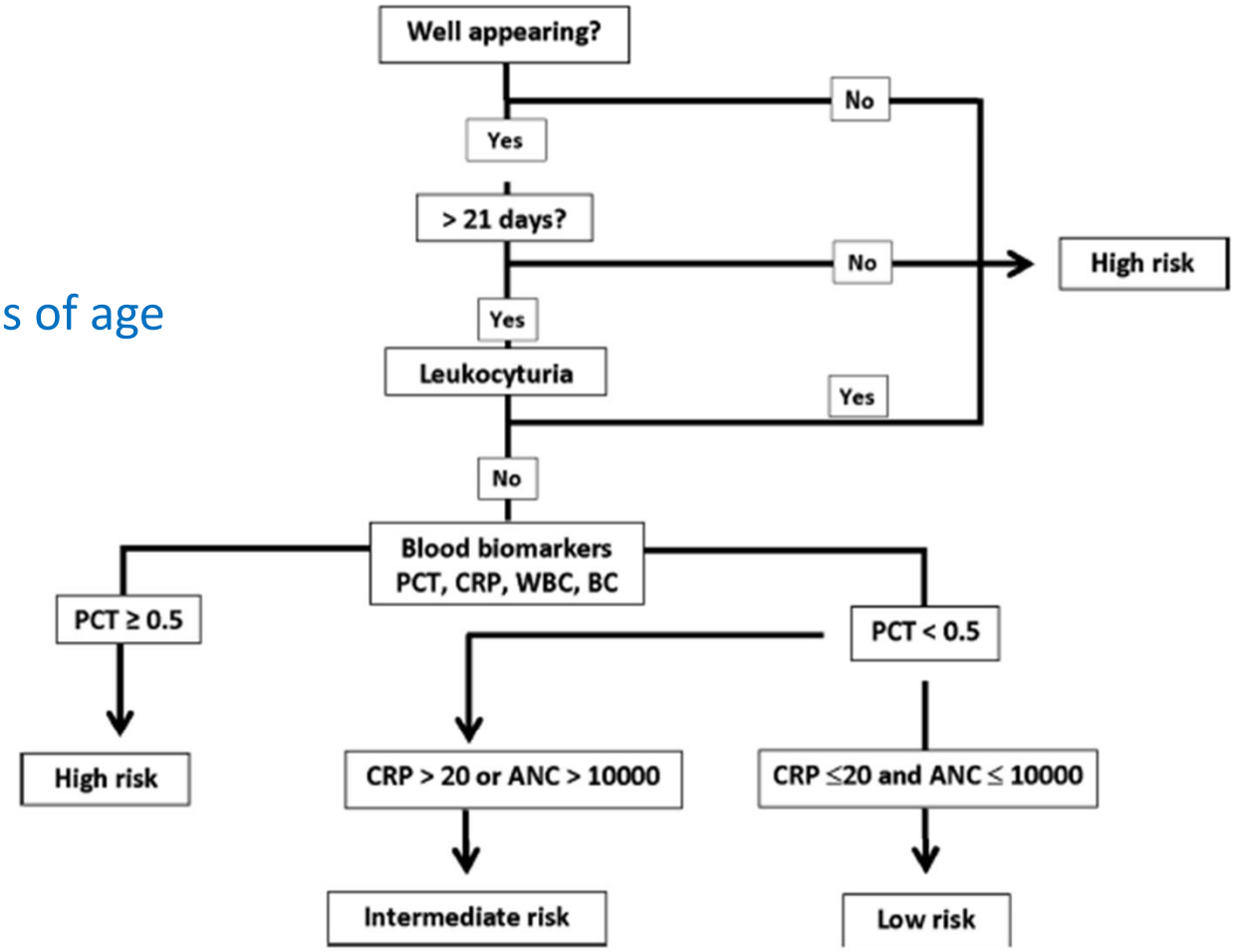
Step-by-Step

- 92% sensitivity **IBI**
- 98% sensitivity **SBI**

- 47% specificity for IBI

Figure 1 Young febrile infants. Step by step approach.



For infants less than 3 months of age

Step-by-Step

- Low risk group = 0.2% (0.7%) IBI
- This sequential approach includes an intermediate-risk group without clear cut management guidance
- Deems all patients with positive urinalysis to be high-risk and requiring LP

Research

JAMA Pediatrics | Original Investigation

A Clinical Prediction Rule to Identify Febrile Infants 60 Days and Younger at Low Risk for Serious Bacterial Infections

Nathan Kuppermann, MD, MPH; Peter S. Dayan, MD, MSc; Deborah A. Levine, MD; Melissa Vitale, MD; Leah Tzimenatos, MD; Michael G. Tunik, MD; Mary Saunders, MD; Richard M. Ruddy, MD; Genie Roosevelt, MD; Alexander J. Rogers, MD; Elizabeth C. Powell, MD, MPH; Lise E. Nigrovic, MD, MPH; Jared Muenzer, MD; James G. Linakis, MD, PhD; Kathleen Grisanti, MD; David M. Jaffe, MD; John D. Hoyle Jr, MD; Richard Greenberg, MD; Rajender Gattu, MD; Andrea T. Cruz, MD, MPH; Ellen F. Crain, MD, PhD; Daniel M. Cohen, MD; Anne Brayer, MD; Dominic Borgialli, DO, MPH; Bema Bonsu, MD; Lorin Browne, DO; Stephen Blumberg, MD; Jonathan E. Bennett, MD; Shireen M. Atabaki, MD, MPH; Jennifer Anders, MD; Elizabeth R. Alpern, MD, MSCE; Benjamin Miller, MS; T. Charles Casper, PhD; J. Michael Dean, MD, MBA; Octavio Ramilo, MD; Prashant Mahajan, MD, MPH, MBA; for the Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network (PECARN)

Supplemental content

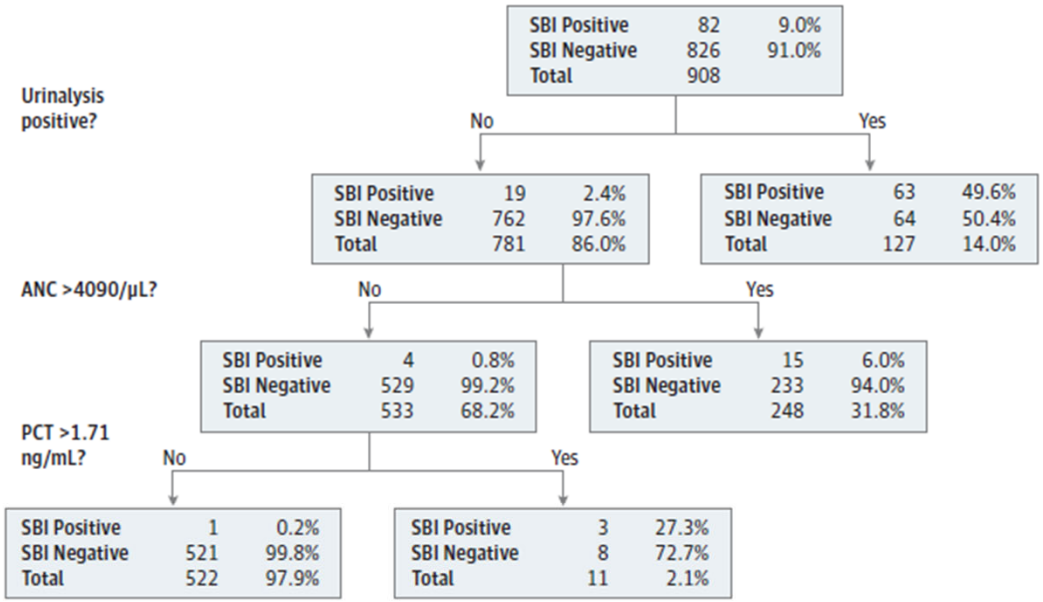
IMPORTANCE In young febrile infants, serious bacterial infections (SBIs), including urinary tract infections, bacteremia, and meningitis, may lead to dangerous complications. However, lumbar punctures and hospitalizations involve risks and costs. Clinical prediction rules using biomarkers beyond the white blood cell count (WBC) may accurately identify febrile infants at low risk for SBIs.

OBJECTIVE To derive and validate a prediction rule to identify febrile infants 60 days and younger at low risk for SBIs.

PECARN (2019)

JAMA Pediatr. 2019;173(4):342-351. doi:10.1001/jamapediatrics.2018.5501
Published online February 18, 2019.

Figure 2. Recursive Partitioning Analysis



	Derivation, No.			Validation, No.		
	SBI	No SBI	Total	SBI	No SBI	Total
SBI per rule	81	305	386	86	330	416
No SBI per rule	1	521	522	2	495	497
Total	82	826	908	88	825	913

	Derivation, No.	Validation, No.
Prediction rule sensitivity (95% CI), %	98.8 (92.5-99.9)	97.7 (91.3-99.6)
Prediction rule specificity (95% CI), %	63.1 (59.7-66.4)	60.0 (56.6-63.3)
Negative predictive value (95% CI), %	99.8 (98.8-100.0)	99.6 (98.4-99.9)
Positive predictive value (95% CI), %	21.0 (17.1-25.5)	20.7 (16.9-25.0)
Negative likelihood ratio (95% CI)	0.02 (0.003-0.14)	0.04 (0.01-0.15)
Positive likelihood ratio (95% CI)	2.68 (2.44 - 2.93)	2.44 (2.23-2.67)

N=1821

Applied recursive analysis to cohort to see what factors were predictive of SBI in well-appearing term infants 60 days and younger

Note their cutoffs:

- ANC > 4090 (Step score 10,000)
- PCT > 1.71 (Step score 0.5)

PECARN

- Low risk group = 0.2% (0.4%) SBI
- Omits CRP
- Again, deems all patients with positive urinalysis to be high-risk and requiring LP

Questions?

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RULE NUMBER 1:
NEVER SET IT TO 2020
imgflip.com

Today:

Incidence of serious bacterial illness in infants less than 60 days old who are relatively well-appearing and have no focal infection:

- UTI – 10%
- Bacteremia – 1 to 3 %
- Meningitis – 0.2 to 1 %

These have not changed for young (less than 60 day old) infants in 30 years – but they have changed dramatically for older infants

Etiology of SBIs in 2021:

Prevalence of Invasive Bacterial Infections in Well-Appearing, Febrile Infants

Russell J. McCulloh, MD,[a,b] Lauren M. McDaniel, MD,[c] Ellen Kerns, PhD, MPH,[a,b] Eric A. Biondi, MD[c]

- Well-appearing febrile infants 7-60do
- 10,618 Pts (75 hospitals)

- Bacteremia 2.4%
  - 1.6% > 1mo

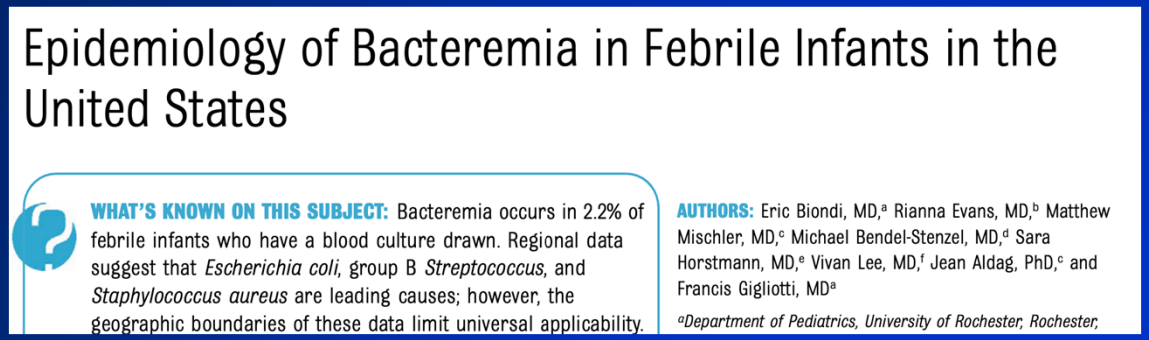
- Meningitis 0.4%
  - 0.2% > 1mo

TABLE 2 Prevalence of Organism by Infection Type

Organism	Bacteremia, *n* (%)	Meningitis, *n* (%)
E coli	121 (48.2)	7 (29.2)
S agalactiae	84 (33.5)	13 (54.2)
Other Gram-negative bacilli[a]	18 (7.2)	0 (0)
Staphylococcus aureus	13 (5.2)	0 (0)
Enterococcus spp.	6 (2.4)	3 (12.5)
viridans streptococci	5 (2.0)	0 (0)
Moraxella catarrhalis	2 (0.8)	0 (0)
Listeria monocytogenes	1 (0.4)	0 (0)
Streptococcus gallolyticus	1 (0.4)	1 (4.2)
Streptococcus pneumoniae	1 (0.4)	0 (0)

[a] *Klebsiella pneumoniae* (*n* = 4); *Klebsiella spp.* (*n* = 3); *Acinetobacter baumanii* (*n* = 3); *Enterobacter aerogenes* (*n* = 3); *Citrobacter fredundii* (*n* = 2); *Enterobacter cloaecae* (*n* = 2); *Salmonella spp.* (*n* = 1)

Etiology of SBIs in 2021:



Epidemiology of Bacteremia in Febrile Infants in the United States

WHAT'S KNOWN ON THIS SUBJECT: Bacteremia occurs in 2.2% of febrile infants who have a blood culture drawn. Regional data suggest that *Escherichia coli*, group B *Streptococcus*, and *Staphylococcus aureus* are leading causes; however, the geographic boundaries of these data limit universal applicability.

AUTHORS: Eric Biondi, MD,[a] Rianna Evans, MD,[b] Matthew Mischler, MD,[c] Michael Bendel-Stenzel, MD,[d] Sara Horstmann, MD,[e] Vivan Lee, MD,[f] Jean Aldag, PhD,[c] and Francis Gigliotti, MD[a]

[a]*Department of Pediatrics, University of Rochester, Rochester,*

Strep pneumonia (and Listeria) rare cause of IBI <2mo

Bacteremia

15% also had UTI (91% if E Coli)

13% also had meningitis (GBS)

Today - Other considerations:

- In general, the older the infant, the better your exam serves as an indicator of serious illness
- The incidence of HSV decreases dramatically with increasing age, starting at 21 days old
- RT-PCR may be a game changer in certain scenarios, although also challenge on how to incorporate into practice due to prolonged viral shedding, especially with rhino/enterovirus

Questions?

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UK febrile infant protocol

Separate pathways for less than 28 days and 29 to 60 days

Focus on ED/initial management

Inpatient arm under development

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UK febrile infant protocol

Goals of pathway

- Unified approach to evaluation of febrile neonates
- Standardization of antimicrobial choices
- Thought tool for clinicians in outlying ERs

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UK febrile infant protocol

Infants **< 28 days** of age all have a full evaluation and are admitted

Infants **29-60 days** are evaluated using a modified Step approach and their risk of SBI is stratified into low, medium and high risk – management varies depending on risk level

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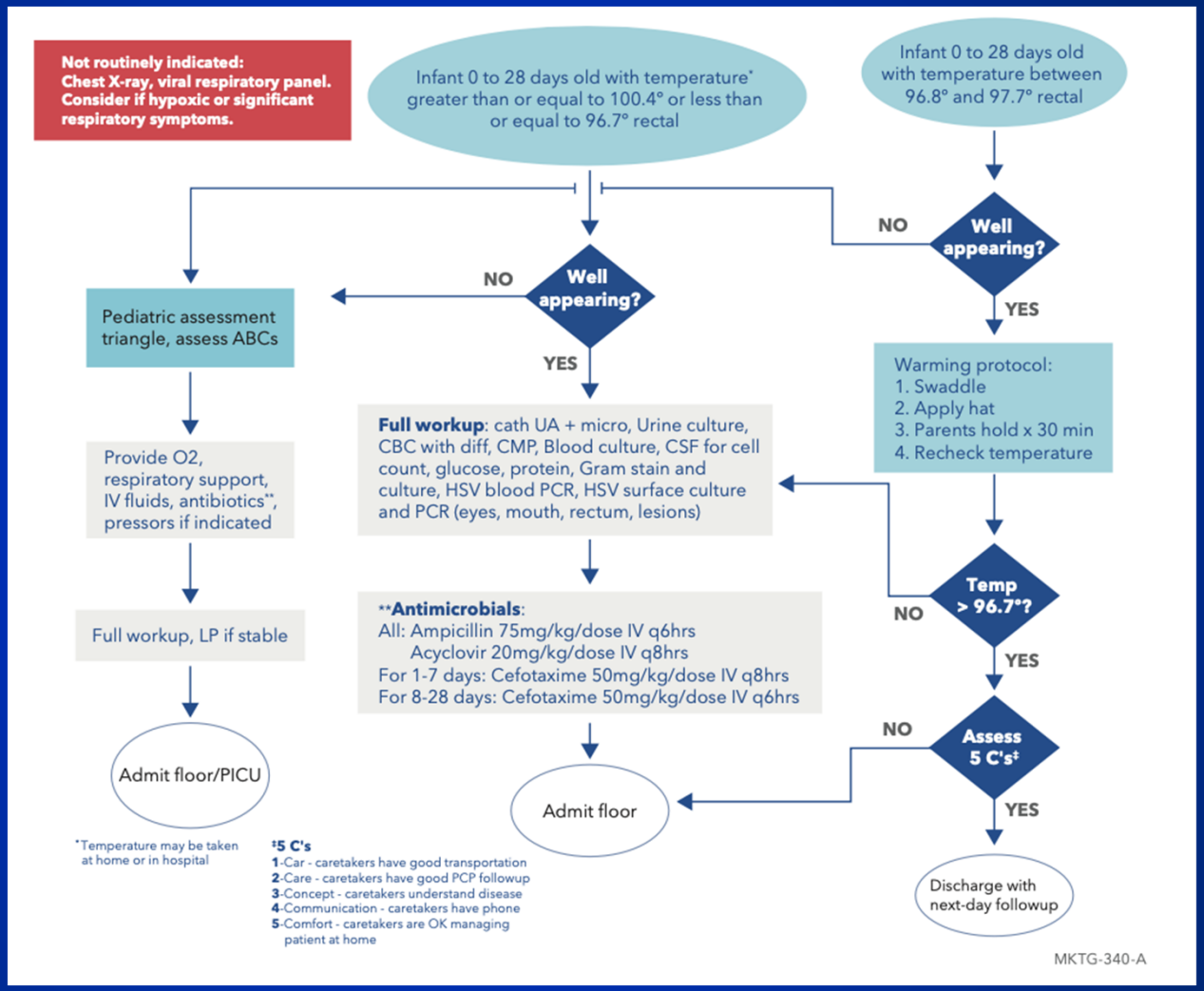
INFANT FEVER/ HYPOTHERMIA PROTOCOL (0-28 DAYS OLD)



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INFANT FEVER/ HYPOTHERMIA PROTOCOL
(0-28 DAYS OLD)

Fever at home?

Risk of Serious Bacterial Infection in Infants Aged ≤60 Days Presenting to Emergency Departments with a History of Fever Only

Sriram Ramgopal, MD[1], Stephen Janofsky, MD[1], Noel S. Zuckerbraun, MD, MPH[1], Octavio Ramilo, MD[2], Prashant Mahajan, MD, MPH, MBA[3], Nathan Kuppermann, MD, MPH[4], and Melissa A. Vitale, MD[1]

- 3825 infants <60d, SBI overall 11.5%

- Fever in ED – SBI 12.8%
- No Fever in ED – **SBI 8.8%**
- **No difference among rates of IBI**

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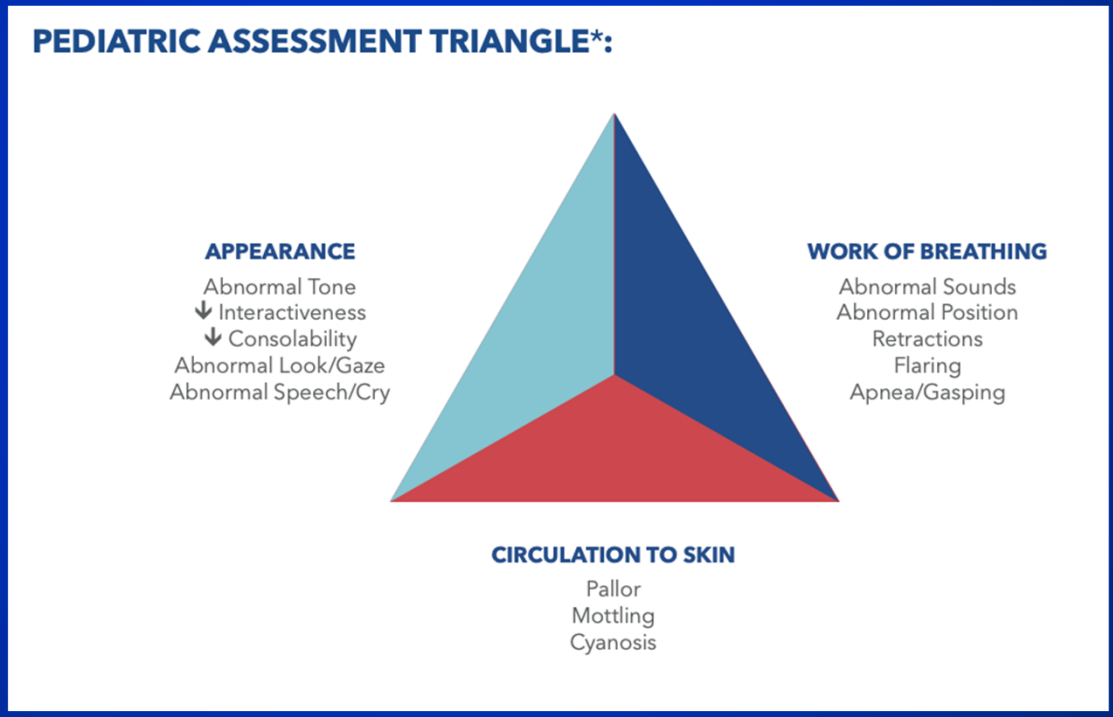
INFANT FEVER/ HYPOTHERMIA PROTOCOL
(0-28 DAYS OLD)

Well-appearing?



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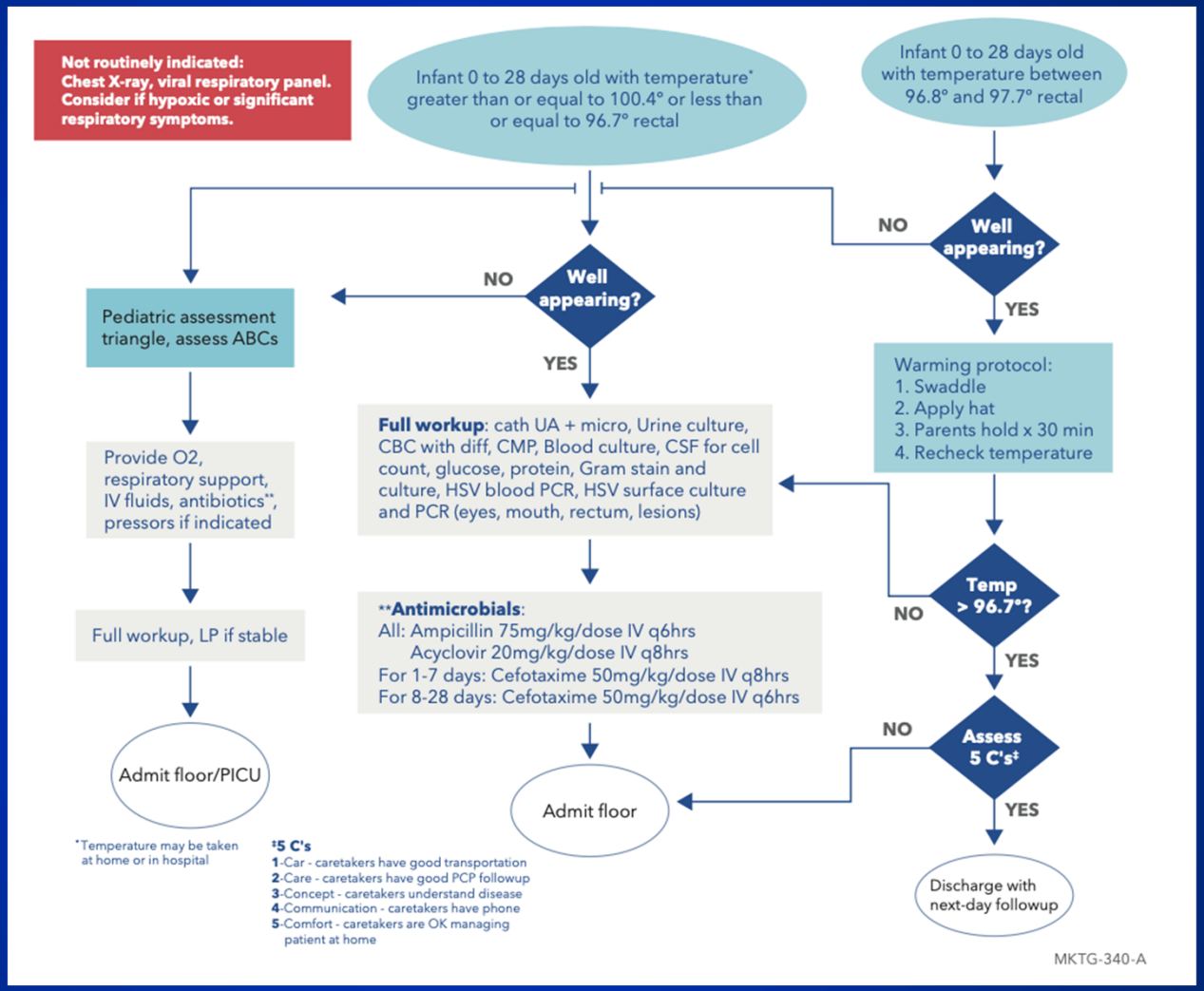
INFANT FEVER/ HYPOTHERMIA PROTOCOL (0-28 DAYS OLD)



0-28 day old pathway specifics

- Complete septic evaluation for all neonates
  - Includes blood, urine and CSF
  - All neonates evaluated and treated for HSV
  - Borderline hypothermic infants given opportunity for re-warming
  - All affected infants will be admitted

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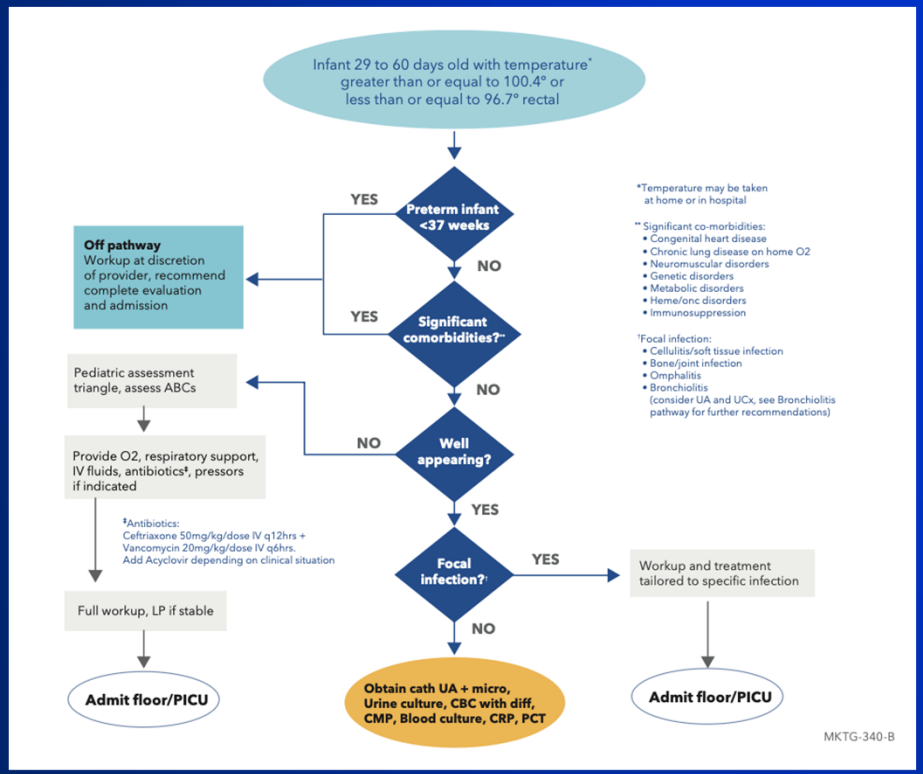
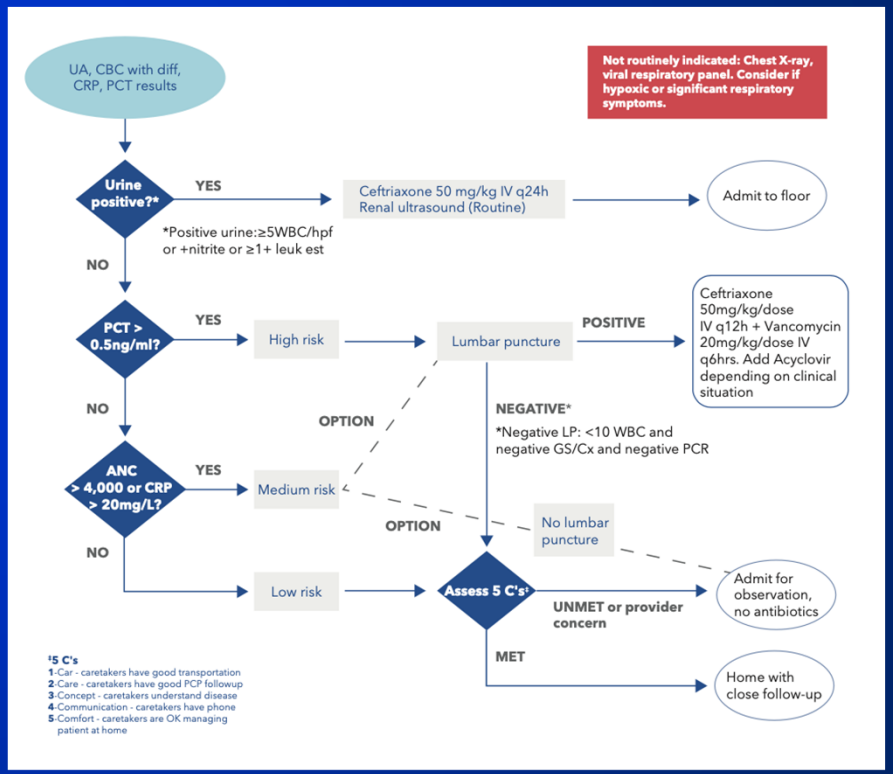
INFANT FEVER/ HYPOTHERMIA PROTOCOL (29-60 DAYS OLD)





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INFANT FEVER/ HYPOTHERMIA PROTOCOL
(29-60 DAYS OLD)

Inclusion/Exclusion

Pre-term

ORIGINAL RESEARCH

Incidence of Serious Bacterial Infections in Ex-premature Infants with a Postconceptional Age Less Than 48 Weeks Presenting to a Pediatric Emergency Department

Nobuaki Inoue, MD*
Tommy Y. Kim, MD*
Anne Marie Birkbeck-Garcia, MD†
Andrew Givner, MD‡
T. Kent Denmark, MD*

* Loma Linda University Medical Center and Children's Hospital, Department of Emergency Medicine, Division of Pediatric Emergency Medicine
† Kaiser Permanente Southern California, Department of Pediatrics
‡ Desert Regional Medical Center, Department of Emergency Medicine

Focal Infection

†Focal infection:
- Cellulitis/soft tissue infection
- Bone/joint infection
- Omphalitis
- Bronchiolitis
  (consider UA and UCx, see Bronchiolitis pathway for further recommendations)

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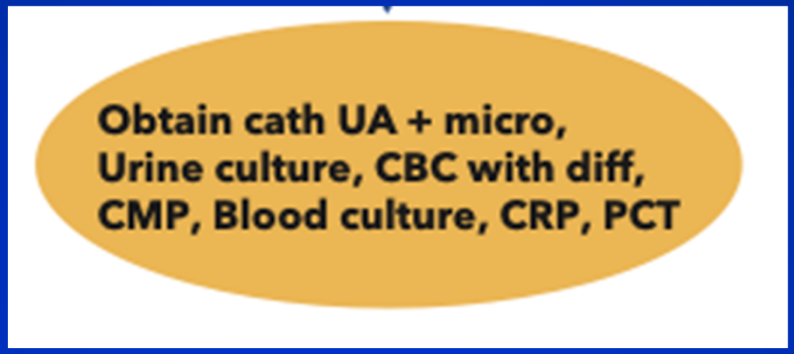
INFANT FEVER/ HYPOTHERMIA PROTOCOL
(29-60 DAYS OLD)



Initial work-up

- Combines Step-by-Step and PECARN

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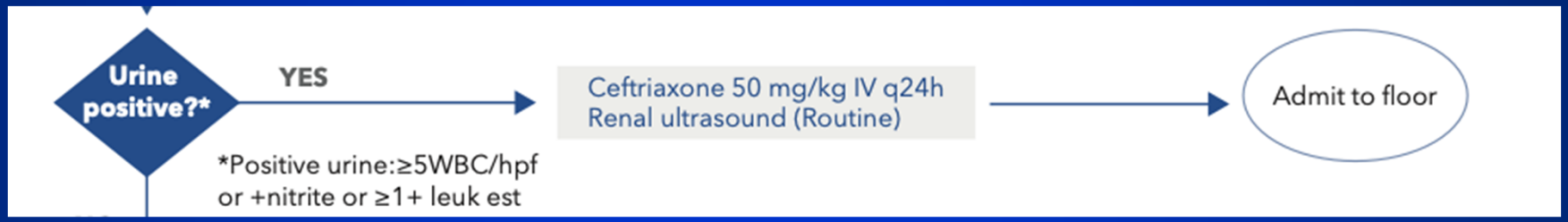
INFANT FEVER/ HYPOTHERMIA PROTOCOL
(29-60 DAYS OLD)



Positive UTI (UA)

- 4 studies on lack of meningitis in well-appearing +UA

Positive UTI (UA)

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INFANT FEVER/ HYPOTHERMIA PROTOCOL
(29-60 DAYS OLD)

ORIGINAL ARTICLES

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Check for updates

Risk of Meningitis in Infants Aged 29 to 90 Days with Urinary Tract Infection: A Systematic Review and Meta-Analysis

James Nugent, MD, MPH[1,2], Molly Childers, MD[3], Nicholas Singh-Miller, MD, PhD[4], Robin Howard, MA[5], Rhonda Allard, MLIS[6], and Matthew Eberly, MD[2]

Original Investigation | Pediatrics

Prevalence of Bacterial Meningitis Among Febrile Infants Aged 29-60 Days With Positive Urinalysis Results
A Systematic Review and Meta-analysis

Brett Burstein, MD, CM, PhD, MPH; Vikram Sabhaney, MD; Jeffrey N. Bone, MSc; Quynh Doan, MD, CM, PhD, MHSc; Fahad F. Mansouri, MD; Garth D. Meckler, MD, MSHS

Testing for Meningitis in Febrile Well-Appearing Young Infants With a Positive Urinalysis

Marie E. Wang, MD, MPH,[a] Eric A. Biondi, MD, MSBA,[b] Russell J. McCulloh, MD,[c] Matthew D. Garber, MD,[d] Beth C. Natt, MD, MPH,[e] Brian P. Lucas, MD, MS,[f] Alan R. Schroeder, MD[a]

CONCOMITANT BACTERIAL MENINGITIS IN INFANTS WITH URINARY TRACT INFECTION

*Joanna Thomson, MD, MPH,**
Andrea T. Cruz, MD, MPH,†
Lise E. Nigrovic, MD, MPH,‡
Stephen B. Freedman, MDCM, MSc,§
Aris C. Garro, MD, MPH,¶ Paul T. Ishimine, MD,‖
*Dina M. Kulik, MD,** Neil G. Uspal, MD,††*
Kendra L. Grether-Jones, MD,‡‡ Aaron S. Miller, MD, MSPH,§§
David Schnadower, MD, MPH,¶¶ and
Samir S. Shah MD, MSCE,‖‖ for the Pediatric Emergency Medicine Collaborative Research Committee (PEM CRC) HSV Study Group*

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INFANT FEVER/ HYPOTHERMIA PROTOCOL
(29-60 DAYS OLD)

Positive UTI (UA)

Original Investigation | Pediatrics

Prevalence of Bacterial Meningitis Among Febrile Infants Aged 29-60 Days With Positive Urinalysis Results
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- Rates of meningitis if +UA = 0.25%
- Rates of meningitis if -UA = 0.28%

- Is positive UTI really a high-risk factor for BM in the **well-appearing** infant?

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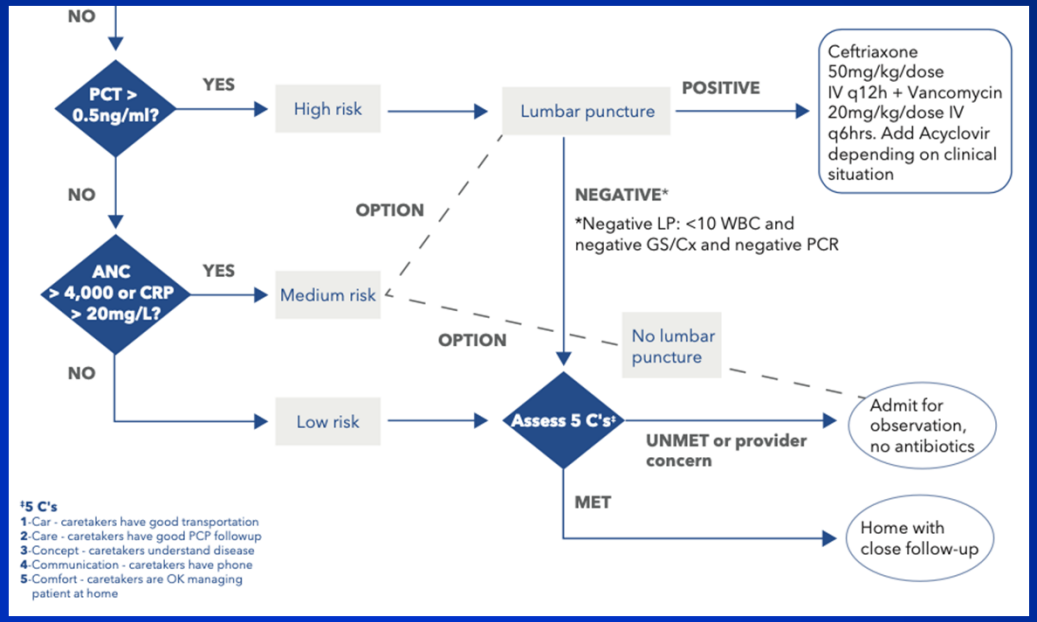
INFANT FEVER/ HYPOTHERMIA PROTOCOL (29-60 DAYS OLD)



High-risk based on PCT (cut-off) gets LP

- Positive LP gets abx + admission
- Negative LP can go home

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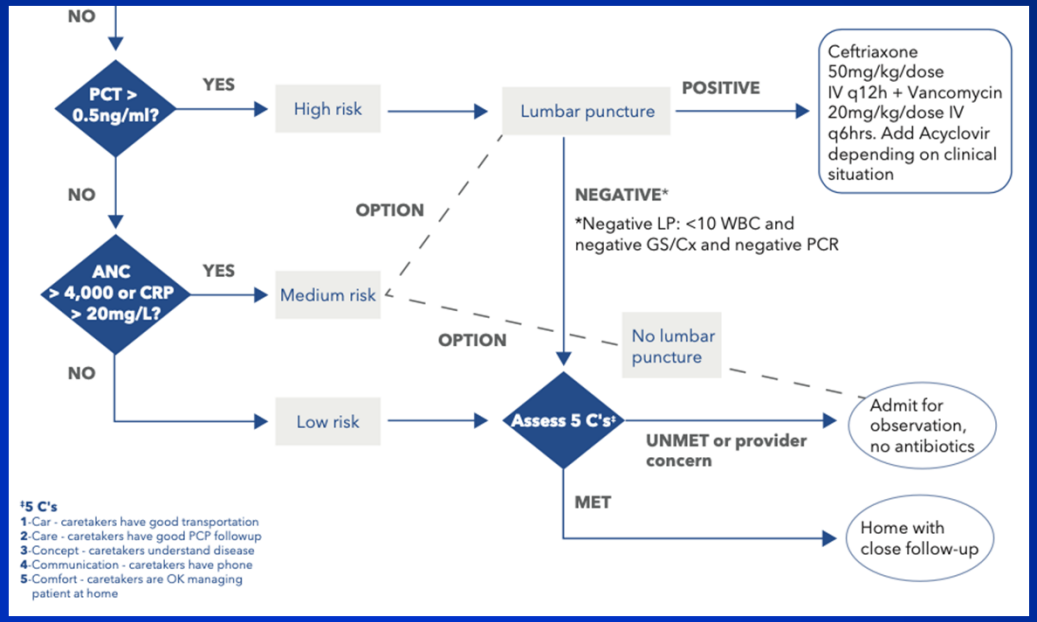

Intermediate-risk based on CRP and ANC (cut-off)

- Option 1 - LP
- Option 2 – Admit for Obs (OFF of abx)

“Maul’s postulates”

- Car, Care, Concept, Communication, Comfort

‡**5 C's**
1-Car - caretakers have good transportation
2-Care - caretakers have good PCP followup
3-Concept - caretakers understand disease
4-Communication - caretakers have phone
5-Comfort - caretakers are OK managing patient at home

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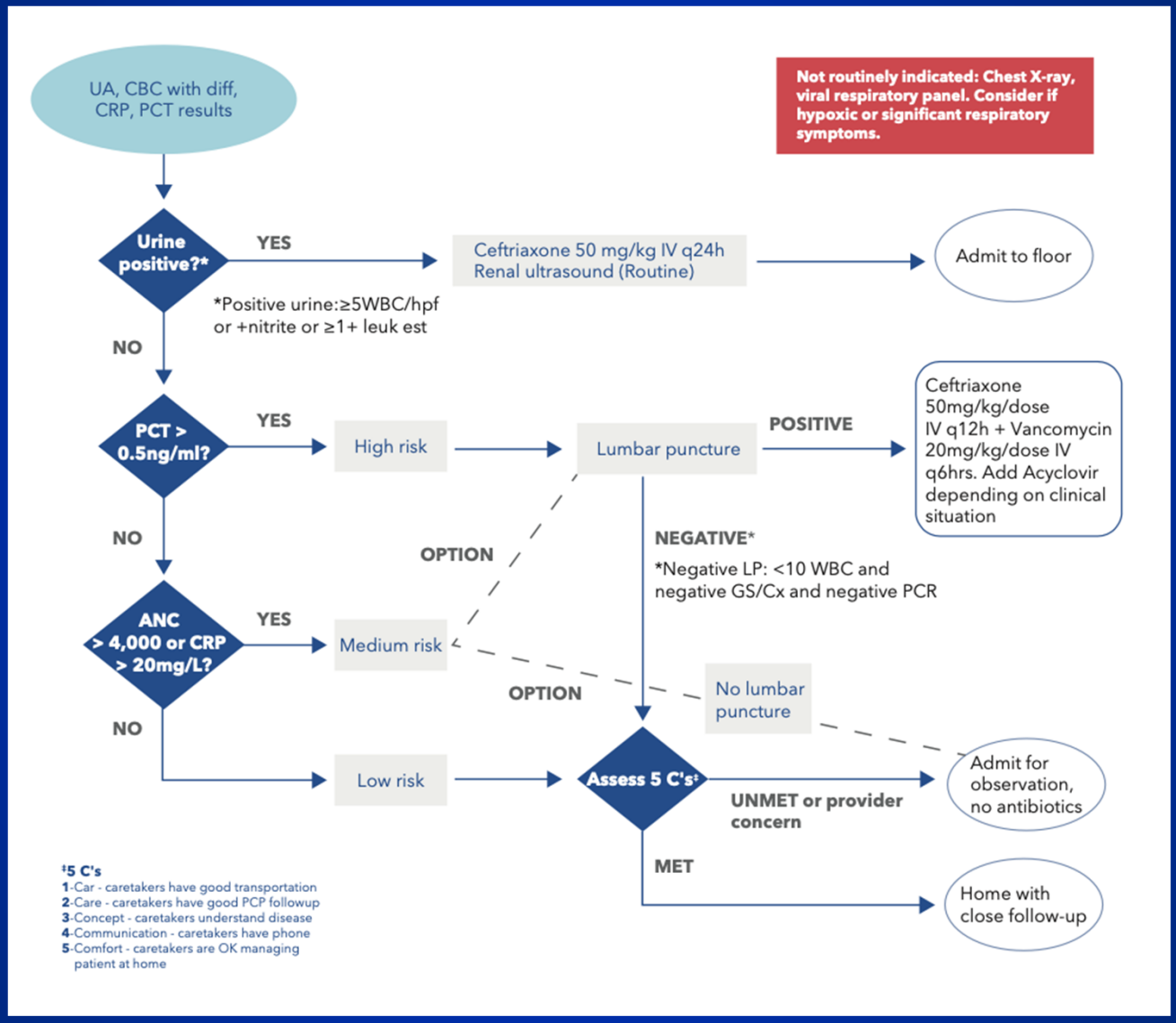
INFANT FEVER/ HYPOTHERMIA PROTOCOL (29-60 DAYS OLD)



Questions?

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CLINICAL PRACTICE GUIDELINE

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old

Robert H. Pantell, MD, FAAP,[a] Kenneth B. Roberts, MD, FAAP,[b] William G. Adams, MD, FAAP,[c] Benard P. Dreyer, MD, FAAP,[d] Nathan Kuppermann, MD, MPH, FAAP, FACEP,[e] Sean T. O'Leary, MD, MPH, FAAP,[f] Kymika Okechukwu, MPA,[g] Charles R. Woods Jr, MD, MS, FAAP[h] SUBCOMMITTEE ON FEBRILE INFANTS

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AAP guideline (2021) - Highlights

- 21 key action items (KAS = key actions statements)
- 3 groupings: 8-21 days, 22-28 days, 29-60 days

- **8-21 days**
  - full septic work-up
  - excludes neonates <7d

- **22-28 days**
  - modified septic work-up using IM (not require LP)
  - if discharged, give Ceftriaxone and re-assess within 24hrs

- **29-60 days**
  - modified septic work-up using IM (not require LP)
  - consideration for PO abx for UTI

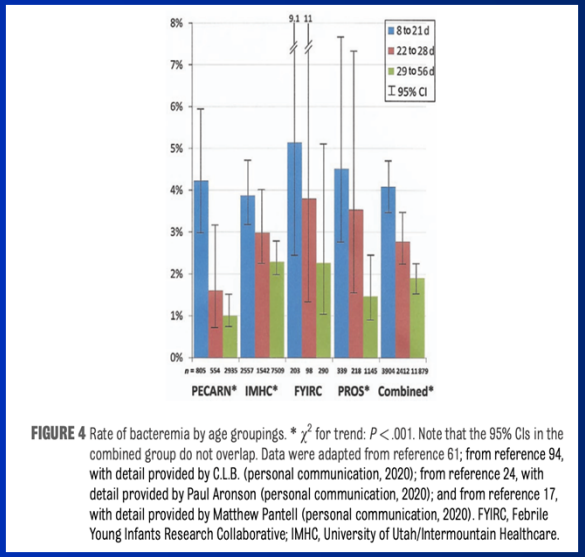

FIGURE 4 Rate of bacteremia by age groupings. * χ^2 for trend: $P < .001$. Note that the 95% CIs in the combined group do not overlap. Data were adapted from reference 61; from reference 94, with detail provided by C.L.B. (personal communication, 2020); from reference 24, with detail provided by Paul Aronson (personal communication, 2020); and from reference 17, with detail provided by Matthew Pantell (personal communication, 2020). FYIRC, Febrile Young Infants Research Collaborative; IMHC, University of Utah/Intermountain Healthcare.

Future Directions

- Quality Improvement
  - Evaluate the diagnostic accuracy of these protocols while ensuring patient safety and avoiding misuse of resources (overall **cost**, ED and hospitalization **length of stay**, **antimicrobial use**, and procedures/**LP**), by assessing them in the pre and post-implementation phases at KCH

- HSV algorithm
- Inpatient arm

- **Community outreach**

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